

## Comparative In Vitro Pharmacodynamics of Imipenem and Meropenem against *Pseudomonas aeruginosa*

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MICs are commonly used to assess the in vitro activities of antimicrobial agents; however, they provide minimal information on the pattern of bacterial activities. Time-kill studies with extensive sampling allow assessment of both the rate and extent of bacterial killing and regrowth. We compared imipenem and meropenem by both MIC-MBC testing and a time-kill study with *P. aeruginosa* 27853. In the time-kill study, concentration/MIC ratios ranging from 0.0625 to 32 times the MIC were studied. The kill rate, time to 99.9% kill, doubling time of regrowth, and area under the bacterial killing curve (AUKC) were evaluated. Degradation during the testing procedure was accounted for by assessing actual drug exposure as determined by the area under the concentration-time curve. Pharmacodynamic parameters were compared by using the Wilcoxon signed-rank test. The modal MIC and MBC for imipenem were 2 and 4 µg/ml, respectively, and those for meropenem were 0.25 and 0.5 µg/ml, respectively. In the time-kill study, both agents displayed concentration-dependent activity over a range of 0.25 to 4 times the MIC. Initial killing (0 to 1 h) was faster with imipenem at the same concentration/MIC ratios ( $P = 0.0506$ ). The time to 99.9% kill was approximately 5 h for both agents. When regrowth occurred, the doubling rate for imipenem, which was the same as that for the growth control, was twice as rapid as that for meropenem. At the same concentrations, the AUKCs over 24 h were lower for meropenem than for imipenem ( $P = 0.0280$ ); however, when normalized by MIC, imipenem resulted in smaller AUKCs. Comparison of plots of area under the concentration-time curve versus AUKC, which accounted for drug degradation and actual drug exposure, revealed that meropenem was three times more active than imipenem, rather than the eightfold difference suggested by MICs. Time-kill curves with extensive sampling and measurement of actual drug exposure, rather than traditional MIC testing, may more accurately assess differences in the in vitro activities of antimicrobial agents.

Since in vitro susceptibility test results have been correlated with clinical outcome (11), these tests are utilized to assess the potential efficacy of an antimicrobial agent and as a method to distinguish between agents with similar antimicrobial spectra. MICs are commonly used to assess the in vitro activity of an antimicrobial agent against a microorganism; however, sole reliance on the MIC may be misleading, since it gives no information regarding the pattern of killing over the time period of the test. Time-kill curves allow one to determine the pattern of bacterial killing and regrowth and allow the calculation of pharmacodynamic parameters such as the rate and extent of killing. A calculated parameter, the area under the bacterial killing curve (AUKC), measures the in vitro effect of an antimicrobial agent for the duration of drug exposure; however, this technique requires frequent sampling and is currently limited to the research setting.

Meropenem, a carbapenem currently in phase III investigational trials, is very similar to imipenem. The two agents have similar pharmacokinetic profiles (1), postantibiotic effects (8, 12), and spectra of activity (9, 20). They display activity against a wide range of aerobic gram-positive, aerobic gram-negative, and anaerobic bacteria. Imipenem appears to be more potent against gram-positive organisms; however, meropenem appears to be more potent against gram-negative organisms, especially

*Pseudomonas aeruginosa*. Affinity for penicillin-binding proteins (PBPs) differs for these agents. Generally, imipenem has high affinity for PBPs 1A and 2. Meropenem also attaches to PBP 2, although its affinity for PBP 3 is much higher than that of imipenem. Attachment of PBP 2 results in the formation of spheroplasts, whereas affinity for PBP 3 results in the development of filamentous forms (19). These differences in affinity for PBPs may explain the differences in the relative potencies of these agents and may affect their pharmacodynamic profiles. Other time-kill studies of imipenem and meropenem with *P. aeruginosa* have demonstrated concentration-dependent killing over a range of 0.5 to 8 times the MIC (5, 21). However, the number of sampling points and range of concentrations studied precluded an accurate assessment of the AUKC or early killing rates as well as the determination of the absolute minimal and maximal effects of these agents. Furthermore, previous studies have not accounted for differences in drug degradation during the testing procedure. Since we have documented the degradation of these agents under in vitro testing conditions (7), we compared imipenem and meropenem in a time-kill study with extensive sampling over a wide concentration range and accounted for drug degradation in the analysis.

### MATERIALS AND METHODS

**Antibiotics, bacterial strain, and media.** Standard laboratory powders of meropenem (ICI Pharmaceuticals, Wilmington, Del.; lot W2675 [expiration date, 2/92]) and imipenem (Merck, Sharp and Dohme, West Point, Pa.; lot 8064T [expiration date, 2/92]) were used in this study. All studies were performed with *P. aeruginosa* ATCC 27853. Mueller-Hinton broth (Difco Laboratories, Detroit, Mich.; lot 0757-01) was prepared immediately prior to use and supplemented with CaCl<sub>2</sub> (25 µg/ml) and MgSO<sub>4</sub> (12.5 µg/ml), according to the guidelines of the National Committee for Clinical Laboratory Standards (NCCLS) (14). An-

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tibiotic-free 15-cm-diameter Mueller-Hinton agar plates (BBL, Cockeysville, Md.) were used for colony count determination.

**MIC-MBC testing.** The MICs and MBCs of meropenem and imipenem against *P. aeruginosa* ATCC 27853 were determined in triplicate on three different occasions. The modal value was used in all subsequent analyses. Stock solutions of imipenem and meropenem were initially prepared in sterile water immediately prior to testing. Subsequent broth standards contained  $\leq 5\%$  water by volume. MICs were determined by the broth microdilution technique according to NCCLS guidelines (14). The MIC was defined as the lowest concentration of antibiotic that completely inhibited the growth of the organism as detected by the unaided eye. Traditional and intermediate twofold dilutions were prepared so that the concentrations studied were 0.5 to 64  $\mu\text{g/ml}$  and 0.375 to 48  $\mu\text{g/ml}$  for imipenem and 0.0625 to 8  $\mu\text{g/ml}$  and 0.047 to 6  $\mu\text{g/ml}$  for meropenem. The final inoculum of approximately  $5 \times 10^5$  CFU/ml was verified with a Spiral Plater (Spiral System Inc., Cincinnati, Ohio). MBCs were determined according to NCCLS guidelines (13), except colony counts were enumerated at 12 to 15 h after plating. The MBC was defined as the lowest antibiotic concentration that decreased the final inoculum by  $\geq 99.9\%$ .

**Time-kill study.** The concentrations studied for imipenem were 64, 32, 16, 8, 4, 2, 1, 0.5, 0.25, and 0.125  $\mu\text{g/ml}$ , while those studied for meropenem were 8, 4, 2, 1, 0.5, 0.25, 0.125, 0.063, 0.031, and 0.016  $\mu\text{g/ml}$ . These concentrations were chosen to create a concentration/MIC ratio range of 0.0625 to 32 times the MIC so that direct comparisons of relationships between concentration and MIC could be performed.

Sterile 96-well microdilution trays (Code a Well Series 200; Plastic Injectors, Inc., Spartanburg, S.C.) were used with a final volume of 100  $\mu\text{l}$  in each well. The final inoculum was prepared according to NCCLS guidelines (14) and verified with the Spiral Plater. An automated inoculator (Gibco Laboratories, Lawrence, Mass.) was used to deliver 50  $\mu\text{l}$  of broth into each well on the plate. A 12-prong multichannel pipette delivered 50  $\mu\text{l}$  of antibiotic into each well in the first column on each plate, and these volumes were twofold diluted by using an automated diluter (Dynatech Laboratories, Inc., Alexandria, Va.). An automated inoculator then delivered the remaining 50  $\mu\text{l}$  of broth or inoculum. All wells in each column contained the same final concentration of antimicrobial agent. The microdilution trays were sealed, continuously shaken on an orbital shaker at 300 rpm, and incubated at 37°C. Identical trays were prepared for each time point so that after sampling the tray could be discarded. Samples were withdrawn at 0, 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 8, 10, 12, 18, and 24 h. At each sampling time, 50  $\mu\text{l}$  was withdrawn from each well in each column by using a 12-prong multichannel pipette (final volume, 600  $\mu\text{l}$ ). The solution was transferred into a sterile container, and 10-fold dilutions were prepared when necessary by withdrawing 100  $\mu\text{l}$  and adding it to 900  $\mu\text{l}$  of normal saline. A 50- $\mu\text{l}$  aliquot of the diluted and/or undiluted samples was plated onto Mueller-Hinton agar plates by using the Spiral Plater. The limit of detection under these conditions was 400 CFU/ml. To minimize antibiotic carryover effects, most samples were diluted at least 10-fold prior to plating; however, undiluted samples were used to determine samples with final colony counts of less than  $4 \times 10^3$  CFU/ml. Comparison of undiluted and diluted samples in this range did not result in differences in colony counts when the counts were corrected for dilution. The plates were incubated for 18 h at 37°C, and surviving colonies were counted. At each time point, the pH of each aliquot was also measured (Corning Ion Analyzer; Corning Glass Works, Corning, N.Y.).

In addition, a separate set of microdilution trays prepared identically to those described above was analyzed over 24 h with a spectrophotometric microplate reader (Biotek EL-320; Biotek Instruments). The optical density was assessed every 2 h at an absorbance wavelength of 562 nm.

**Data analysis.** The time-kill data were plotted as the number of surviving organisms (CFU per milliliter) versus time. For the calculation of pharmacodynamic parameters, all datum points were utilized. Killing rates between 0 and 1 h, which served as a measure of antibacterial activity, were determined by simple linear regression of the  $\log_{10}$  CFU per milliliter versus time. In all instances in which a kill rate could be calculated, three data points were used. From the surviving colony counts, the time at which 99.9% killing of the initial inoculum occurred was determined from these plots.

The rate of growth for the control curve and regrowth in the time-kill plots were determined by using the following equations for doubling time (2):  $d = \ln 2/u$ ;  $\mu = (\ln C - \ln C_0)/(t - t_0)$ , where  $C_0$  is the CFU per milliliter at time  $t_0$  and  $C$  is the CFU per milliliter at time  $t$ .

The AUKC was calculated by using the linear trapezoidal rule between all sampling time points. The AUKC<sub>0-1</sub> and AUKC<sub>0-24</sub> were the sum of the areas from time 0 to 1 h and the sum of the individual areas over the entire 24-h sampling period, respectively.

The area under the concentration-time curve (AUC) was calculated by using the linear trapezoidal rule. Since both of these drugs have been shown to degrade in Mueller-Hinton broth at 37°C, the AUC<sub>0-24</sub> was calculated by using actual assayed concentrations at each time point (7).

Statistical comparisons between imipenem and meropenem were performed by using the Wilcoxon signed-rank test. Comparisons were performed for the pharmacodynamic parameters resulting from the same concentrations of both drugs (0.125 to 8  $\mu\text{g/ml}$ ) and the same concentration/MIC ratios (0.0625 to 32 times the MIC).

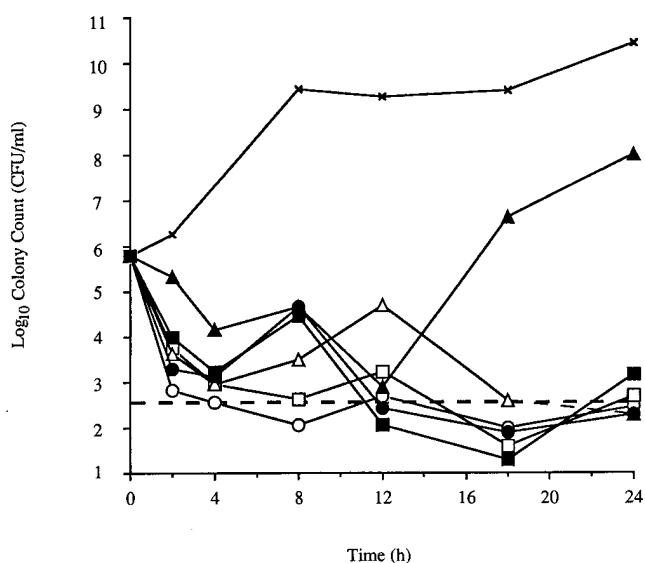


FIG. 1. Time-kill plots for imipenem and meropenem above the MIC. ○, imipenem at 32 times the MIC (64  $\mu\text{g/ml}$ ); ●, meropenem at 32 times the MIC (8  $\mu\text{g/ml}$ ); □, imipenem at 8 times the MIC (16  $\mu\text{g/ml}$ ); ■, meropenem at 8 times the MIC (2  $\mu\text{g/ml}$ ); △, imipenem at 2 times the MIC (4  $\mu\text{g/ml}$ ); ▲, meropenem at 2 times the MIC (0.5  $\mu\text{g/ml}$ ); ×, growth control. The dotted line indicates the limit of detection.

## RESULTS

**MIC-MBC testing.** By traditional twofold dilutions, the MICs of imipenem and meropenem were 2 and 0.25  $\mu\text{g/ml}$  and the MBCs were 4 and 0.5  $\mu\text{g/ml}$ , respectively. By intermediate dilution, the MICs were 3 and 0.375  $\mu\text{g/ml}$  and the MBCs were 3 and 0.75  $\mu\text{g/ml}$  for imipenem and meropenem, respectively.

**Time-kill plots.** For clarity, only data from every other drug concentration at 0, 2, 4, 8, 12, 18, and 24 h are graphically displayed. Both agents demonstrated killing of approximately 3 to 4 log units (Fig. 1 and 2). It appeared that bacterial killing was multiphasic for both imipenem and meropenem; however, the number of data points precluded an accurate assessment of these kill rates. Regrowth occurred with both agents at concentrations at and below the MIC and reached a plateau at approximately  $10^9$  CFU/ml. Regrowth was slower for meropenem than for imipenem, with median doubling times of 0.38 and 0.73 h for imipenem and meropenem, respectively. The doubling rate for the growth control was 0.39 h. At concentrations above the MIC, killing was maintained throughout the 24-h study period, with the exception of meropenem at 0.5  $\mu\text{g/ml}$  (2 times the MIC).

Over the concentration ranges for both imipenem and meropenem, the pH was 7.2 at the time of maximal bacterial killing and increased to 7.4 when regrowth reached a plateau. Following exponential growth in the growth control, the pH increased to a maximum of 7.9.

Concentration-dependent activity over approximately the same range of concentrations of imipenem and meropenem as shown with the colony counts was demonstrated with absorbance values (data not shown). However, prior to 3 h, drug effects were undetectable, and the spectrophotometric data represent either morphologic changes or regrowth after early bacterial killing.

**Pharmacodynamic parameter analysis.** As seen in Tables 1 and 2, the median time to reach 99.9% killing of the initial inoculum was approximately 5 h and was similar for the two

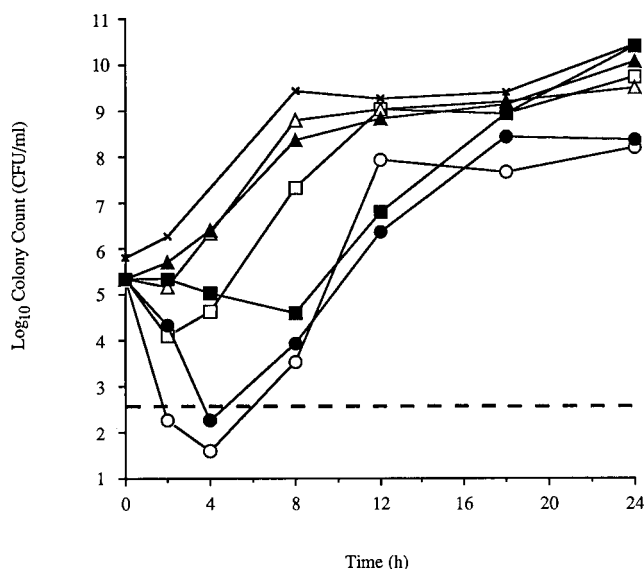


FIG. 2. Time-kill plots for imipenem and meropenem at and below the MIC. ○, imipenem at the MIC (2 µg/ml); ●, meropenem at the MIC (0.25 µg/ml); □, imipenem at 1/4 of the MIC (0.5 µg/ml); ■, meropenem at 1/4 of the MIC (0.0625 µg/ml); △, imipenem at 1/16 of the MIC (0.125 µg/ml); ▲, meropenem at 1/16 of the MIC (0.0156 µg/ml); ×, growth control. The dotted line indicates the limit of detection.

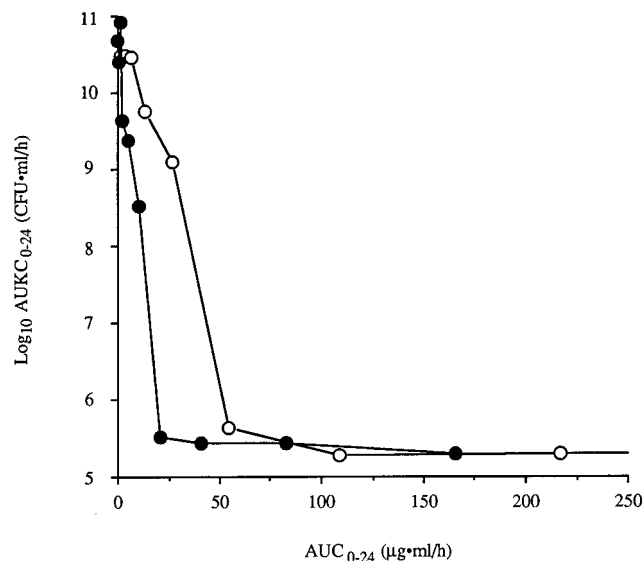


FIG. 3.  $AUC_{0-24}$  for imipenem (○) and meropenem (●) versus effect ( $AUKC_{0-24}$ ).

agents whether they were evaluated at the same absolute concentration or the same concentration/MIC ratio. There was no difference in the kill rate from 0 to 1 h between imipenem and meropenem when they were evaluated at the same absolute concentrations (Table 1); however, as shown in Table 2, at the same concentration/MIC ratio, imipenem was more rapidly bactericidal ( $P = 0.0506$ ). The  $AUKC_{0-1}$  was smaller (indicating greater bactericidal activity) for imipenem at the same concentration/MIC ratio ( $P = 0.0069$ ). In the  $AUKC_{0-24}$  analysis, which may incorporate regrowth of the organism, the median AUKC was larger for imipenem at the same concentration ( $P = 0.0280$ ). However, at the same concentration/MIC ratio, the AUKC was smaller for imipenem. It should be noted that although samples below the theoretical limit of detection were included in the  $AUKC_{0-24}$  analysis, their contribution to the AUKC was negligible.

Concentration-dependent bactericidal activity was seen with both imipenem and meropenem (Fig. 3 and 4). Both agents achieved maximal bactericidal activity at the same  $AUKC_{0-24}$ ; however, meropenem had maximal activity at a three- to four-fold lower AUC (Fig. 3). When normalized for the traditional twofold dilution MIC (AUC/MIC), imipenem displayed a steeper concentration-effect curve, was slightly more active (lower AUKC), and reached its maximum effect at an  $AUC_{0-24}$

$24/MIC$  ratio of approximately 30. Meropenem displayed concentration-dependent activity over a wider range and reached the maximum effect at an  $AUC_{0-24}/MIC$  ratio of approximately 80 (Fig. 4). The use of intermediate-dilution MICs would produce the same relative differences in these relationships for imipenem and meropenem.

## DISCUSSION

β-Lactams are not considered to display concentration-dependent activity; however, this usually refers to activity at concentrations above the MIC. This study verifies the findings of others which demonstrated concentration-dependent activity of imipenem and meropenem over a range of concentrations (5, 21). For both drugs, concentrations of  $\geq 4$  times the MIC resulted in killing of 3 log units that was maintained for 24 h. In contrast, Flukiger et al. (6) observed no concentration-dependent killing by imipenem of *P. aeruginosa* when comparing concentrations of 2 and 10 times the MIC. We noted substantial regrowth at the MIC; however, at two times the MIC, regrowth was observed only with meropenem. When regrowth occurred, it occurred earlier and was more rapid with imipenem. The doubling time of imipenem-exposed *P. aeruginosa* was virtually identical to that of the growth control. These concentration-dependent effects on regrowth were verified by the spectrophotometric analysis. Other investigators have demonstrated effects of carbapenems at concentrations below the MIC (15, 21). Our findings were similar, with demonstrable

TABLE 1. Comparison of pharmacodynamic parameters evaluated at the same drug concentrations<sup>a</sup>

Antimicrobial agent	Time to 99.9% kill (h) <sup>b</sup>	Kill rate from 0 to 1 h (h <sup>-1</sup> ) <sup>c</sup>	$AUKC_{0-1}$ (CFU · h/ml, 10 <sup>5</sup> ) <sup>d</sup>	$AUKC_{0-24}$ (CFU · h/ml, 10 <sup>5</sup> ) <sup>d</sup>
Imipenem	5.5 (2.0–6.0)	3.5 (0.8–5.5)	1.37 (0.64–1.80)	58,400 (1.94–302,000)
Meropenem	4.5 (4.5–5.0)	3.6 (1.9–5.7)	2.14 (1.01–2.68)	3.38 (1.98–43,200) <sup>e</sup>

<sup>a</sup> All data presented as medians with ranges in parentheses.

<sup>b</sup>  $n = 3$  (2 to 8 µg/ml).

<sup>c</sup>  $n = 6$  (0.25 to 8 µg/ml).

<sup>d</sup>  $n = 7$  (0.125 to 8 µg/ml).

<sup>e</sup>  $P = 0.0280$ .

TABLE 2. Comparison of pharmacodynamic parameters evaluated at the same concentration/MIC ratios<sup>a</sup>

Antimicrobial agent	Time to 99.9% kill (h) <sup>b</sup>	Kill rate from 0 to 1 h (h <sup>-1</sup> ) <sup>c</sup>	AUKC <sub>0-1</sub> (CFU · h/ml, 10 <sup>5</sup> ) <sup>d</sup>	AUKC <sub>0-24</sub> (CFU · h/ml, 10 <sup>5</sup> ) <sup>d</sup>
Imipenem	5.5 (3.0–6.0)	4.9 (0.8–5.6) <sup>e</sup>	1.64 (0.64–1.80) <sup>f</sup>	6,350 (1.72–302,000)
Meropenem	5.0 (4.5–10.0)	1.9 (1.3–5.7)	1.71 (1.01–2.68)	13,400 (1.98–813,000)

<sup>a</sup> All data are presented as medians, with ranges in parentheses.<sup>b</sup> *n* = 5 (2 to 32 times the MIC).<sup>c</sup> *n* = 9 (0.125 to 32 times the MIC).<sup>d</sup> *n* = 10 (0.0625 to 32 times the MIC).<sup>e</sup> *P* = 0.0506.<sup>f</sup> *P* = 0.0069.

concentration-dependent activity at concentration/MIC ratios of as low as 0.25 times the MIC for both agents.

Traditionally, the MIC and/or MBC has been used to assess the in vitro activities of antimicrobial agents. However, these measurements are taken at a fixed time (usually 18 h) after the initiation of drug exposure and fail to assess the effects of initial bacterial killing rates or varying rates of regrowth. Time-kill curves allow one to assess both the AUKC as a measure of overall drug exposure effects and killing rates early after the initiation of drug exposure. Several studies have correlated the rate of in vitro bactericidal killing to outcome in animal models of infection. Drake and coworkers (3) found that the in vitro rates of killing of *Staphylococcus aureus* were faster with nafcillin in combination with either gentamicin or tobramycin than with nafcillin alone. When these drugs were used in a rabbit model of *S. aureus* endocarditis, nafcillin plus either aminoglycoside resulted in lower colony counts in vegetations than nafcillin alone. Potel et al. (16) reported similar findings in an animal model of gram-negative endocarditis in which outcome was correlated with the in vitro killing rate. In a rabbit model of *Escherichia coli* endocarditis in which single daily doses of aminoglycosides, fluoroquinolones, and  $\beta$ -lactams were studied, the in vitro killing rate at 3 h was correlated with outcome. As others have shown, fluoroquinolones and aminoglycosides in that animal model displayed more rapid killing than  $\beta$ -lactams (17). Eng et al. (4) evaluated organisms from patients with gram-negative bacillary meningitis and found that

the MIC and MBC were poor predictors of outcome. In patients treated with ceftriaxone, cefotaxime, or moxalactam, more rapid in vitro killing was correlated with a better clinical outcome. Similar to other results (5, 21), both imipenem and meropenem in our study demonstrated multiphasic killing rates; however, the initial killing rate (0 to 1 h) was faster with imipenem. The median time to 99.9% kill of the initial inoculum was approximately the same for both agents; however, when this was achieved, it occurred within 6 and 10 h for imipenem and meropenem, respectively. These differences may be explained by the relative affinities for PBPs 2 and 3 and the development of filamentous forms with meropenem (19).

Animal and human studies have shown that the length of time that the concentration of a  $\beta$ -lactam in serum remains above the MIC is the pharmacodynamic parameter that is the best predictor of clinical outcome (10, 18). This parameter is difficult to assess in in vitro tests such as MIC and time-kill tests that involve fixed concentrations of antimicrobial agents. Although it is usually assumed that this initial drug concentration is maintained throughout the test, we have documented degradation of imipenem and meropenem during time-kill testing (7). This decline in drug concentration during the test allows one to calculate the length of time that the drug concentration remains above the MIC; however, the twofold dilutions utilized in this study limited this analysis. Since the MIC of imipenem was 2  $\mu$ g/ml, initial imipenem concentrations of  $\leq 2$   $\mu$ g/ml remained at or below the MIC for the duration of the time-kill test. Since the half-life of degradation of imipenem was approximately 14 h, all initial imipenem concentrations above 8  $\mu$ g/ml remained above the MIC for the duration of the test (24 h). Therefore, only the initial concentration of 4  $\mu$ g/ml, for which the time that the drug concentration remained above the MIC was 14 h, revealed any information concerning the effect of the time that the concentration remained above the MIC. With this concentration, the AUKC was only slightly higher than that seen with initial concentrations of  $\geq 8$   $\mu$ g/ml. Because of the slower rate of degradation with meropenem (half-life of approximately 38 h), initial concentrations of  $\geq 0.5$   $\mu$ g/ml remained above the MIC, whereas concentrations of  $\leq 0.25$   $\mu$ g/ml were at or below the MIC for the entire 24-h period. Thus, effects of time that the drug concentration remained above the MIC with meropenem could not be assessed.

The AUC allows one to measure drug exposure during an in vitro test. If drug concentrations are constant throughout the test, the AUC would not provide any information different from the initial drug concentration, since it would simply result from multiplying the concentration by the length of time of the test. However, since drug concentrations declined during the test, the AUC would assess drug exposure more accurately than the initial drug concentration. When the AUCs of imipenem and meropenem were plotted against the AUKCs, meropenem was only three times more active than imipenem;

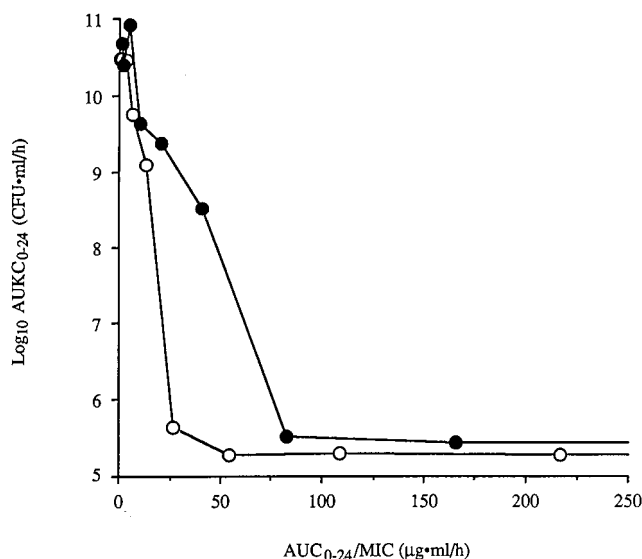


FIG. 4. AUC<sub>0-24</sub>/MIC ratios for imipenem (○) and meropenem (●) versus effect (AUKC<sub>0-24</sub>).

however, when correction for degradation is not done, it appears that meropenem is at least four times more active than imipenem. These plots of AUC versus AUKC represent the effects of actual drug exposure over time and are likely indicative of the true differences in potency between these two agents as opposed to simply comparing MBCs. Moreover, if one used MIC results to compare these agents, meropenem would appear to be eight times more active than imipenem.

In summary, meropenem and imipenem both display concentration-dependent activity over a wide range of concentrations below the MIC and up to fourfold above the MIC. Imipenem kills at a faster initial rate than meropenem; however, both maintain killing of  $\geq 3$  log units at concentrations of  $\geq 4$  times the MIC. With correction for the differences in drug degradation and measurement of the effects of drug exposure with the AUKC, meropenem appears to be approximately three times more potent than imipenem against this strain of *P. aeruginosa*, rather than the eightfold difference suggested by MIC testing.

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#### REFERENCES

1. Bax, R. P., W. Bastain, A. Featherstone, D. M. Wilkinson, M. Hutchison, and S. J. Haworth. 1989. The pharmacokinetics of meropenem in volunteers. *J. Antimicrob. Chemother.* **24**(Suppl. A):311–320.
2. Carlberg, D. M. 1986. Determining the effects of antibiotics on bacterial growth by optical and electrical methods, p. 65. In V. Lorian (ed.), *Antibiotics in laboratory medicine*, 2nd ed. The Williams & Wilkins Co., Baltimore.
3. Drake, T. A., C. J. Hackbarth, and M. A. Sande. 1983. Value of serum tests in combined drug therapy of endocarditis. *Antimicrob. Agents Chemother.* **24**:653–657.
4. Eng, R. H. K., C. Cherubin, S. M. Smith, and F. Buccini. 1984. Examination of gram-negative bacilli from meningitis patients who failed or relapsed on moxalactam therapy. *Antimicrob. Agents Chemother.* **26**:850–856.
5. Ferrara, A., G. Grassi, F. A. Grassi, P. D. Piccioni, and G. G. Grassi. 1989. Bactericidal activity of meropenem and interactions with other antibiotics. *J. Antimicrob. Chemother.* **24**(Suppl. A):239–250.
6. Flukiger, U., C. Segessenmann, and A. U. Gerber. 1991. Integration of pharmacokinetics and pharmacodynamics of imipenem in a human-adapted mouse model. *Antimicrob. Agents Chemother.* **35**:1905–1910.
7. Friedrich, L. V., R. L. White, D. S. Burgess, D. I. Warkentin, and J. A. Bosso. 1995. Comparative stability of imipenem and meropenem in Mueller-Hinton broth at room temperature, during incubation, and during frozen storage. *J. Infect. Dis. Pharmacother.* **1**:21–34.
8. Gudmundsson, S., B. Vogelmann, and W. A. Craig. 1986. The in-vivo post-antibiotic effect of imipenem and other new antimicrobials. *J. Antimicrob. Chemother.* **18**(Suppl. E):67–73.
9. Jones, R. N., K. E. Aldridge, S. D. Allen, A. L. Barry, P. C. Fuchs, E. H. Gerlach, and M. A. Pfaller. 1989. Multicenter in vitro evaluation of SM-7338, a new carbapenem. *Antimicrob. Agents Chemother.* **33**:562–565.
10. Leggett, J. E., B. Fantin, S. Ebert, K. Totsuka, B. Vogelmann, W. Calame, H. Mattie, and W. A. Craig. 1989. Comparative antibiotic dose-effect relations at several dosing intervals in murine pneumonitis and thigh-infection models. *J. Infect. Dis.* **159**:281–292.
11. Lorian, V., L. Burns, and J. Ernst. 1990. Predictive values of susceptibility tests for the outcome of antibiotic therapy. *J. Antimicrob. Chemother.* **25**:175–181.
12. Nadler, H. L., D. H. Pitkin, and W. Sheikh. 1989. The postantibiotic effect of meropenem and imipenem on selected bacteria. *J. Antimicrob. Chemother.* **24**(Suppl. A):225–231.
13. National Committee for Clinical Laboratory Standards. 1987. M26-P. Methods for determining bactericidal activity of antimicrobial agents. National Committee for Clinical Laboratory Standards, Villanova, Pa.
14. National Committee for Clinical Laboratory Standards. 1990. Approved standard M7-A2. Methods for dilution antimicrobial susceptibility tests for bacteria that grow aerobically. National Committee for Clinical Laboratory Standards, Villanova, Pa.
15. Odenholt-Tornqvist, I. 1993. Studies on the postantibiotic effect and the postantibiotic sub-MIC effect of meropenem. *J. Antimicrob. Chemother.* **31**:881–892.
16. Potel, G., J. Caillon, B. Fantin, J. Raza, F. Le Gallou, J. Y. Lepage, P. Le Conte, D. Bugnon, D. Baron, and H. B. Drugeon. 1991. Impact of dosage schedule on the efficacy of gentamicin, tobramycin, or amikacin in an experimental model of *Serratia marcescens* endocarditis: in vitro-in vivo correlation. *Antimicrob. Agents Chemother.* **35**:111–116.
17. Potel, G., N. P. Chau, B. Pangon, B. Fantin, J. M. Vallois, F. Faurisson, and C. Carbon. 1991. Single daily dosing of antibiotics: importance of in vitro killing rate, serum half-life, and protein binding. *Antimicrob. Agents Chemother.* **35**:2085–2090.
18. Schentag, J. J. 1992. Pharmacokinetics and pharmacodynamics of beta-lactam antibiotics. *Infect. Med.* **9**(Suppl B):10–12.
19. Sumita, Y., M. Fukasawa, and T. Okuda. 1990. Comparison of two carbapenems, SM-7338 and imipenem: affinities for penicillin-binding proteins and morphological changes. *J. Antibiot.* **43**:314–320.
20. Visser, M. R., I. M. Hoepelman, H. Beumer, M. Rozenberg-Arska, and J. Verhoef. 1989. Comparative in vitro antibacterial activity of the new carbapenem meropenem (SM-7338). *Eur. J. Clin. Microbiol. Infect. Dis.* **8**:1061–1064.
21. Yourassowsky, E., M. P. Van der Linden, M. J. Lismont, F. Crokaert, and Y. Glupczynski. 1989. Bactericidal activity of meropenem against *Pseudomonas aeruginosa*. *J. Antimicrob. Chemother.* **24**(Suppl. A):169–174.